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OH-Radical Specific Addition to Glutathione S-Atom at the Air–Water Interface: Relevance to the Redox Balance of the Lung Epithelial Lining Fluid

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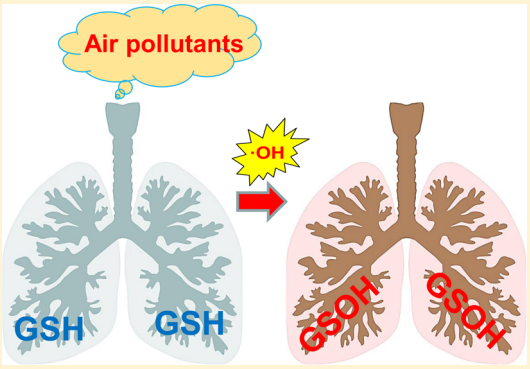
Supporting Information

ABSTRACT: Antioxidants in epithelial lining fluids (ELF) prevent inhaled air pollutants from reaching lung tissue. This process, however, may upset ELF's redox balance, which is deemed to be expressed by the ratio of the major antioxidant glutathione (GSH) to its putative oxidation product GSSG. Previously, we found that at physiological pH O_3(g) rapidly oxidizes GS^{2-}(aq) (but not GSH^-) to GSO_3^- rather than GSSG. Here, we report that in moderately acidic pH ≤ 5 media ·OH(g) oxidizes GSH^-(aq) to sulfenic $GSOH^-$, sulfinic GSO_2^-, and sulfonic GSO_3^- acids via ·OH specific additions to reduced S-atoms. The remarkable specificity of ·OH on water versus its lack of selectivity in bulk water implicates an unprecedented steering process during [OH···GSH] interfacial encounters. Thus, both O_3 and ·OH oxidize GSH to $GSOH^-$ under most conditions, and since $GSOH^-$ is reduced back to GSH in vivo by NADPH, redox balance may be in fact signaled by GSH/GSOH ratios.



How to cope with the detrimental effects of air pollution on human health and quality of life in ever-expanding megacities is a pressing, complex issue.[1−4] Decades after the implementation of environmental controls, O_3 and $PM_{2.5}$ (≤2.5 μm diameter particulate matter) concentrations significantly exceed standard limits in cities worldwide.[5−8] Numerous studies have shown that premature mortality[9,10] and all-cause (AC),[2] but particularly cardiorespiratory[11] acute and chronic health effects display statistically significant positive correlations with ambient O_3 and $PM_{2.5}$ concentrations.[4,10,12,13] A rigorous statistical analysis of air pollution data and age-specific cardiovascular (CV) and AC premature mortality rates for 483 counties in 15 US states from 2000 to 2010 confirmed positive associations between $PM_{2.5}$ and O_3 and between the levels of both pollutants with CV and AC mortality rates. However, it revealed that the ∼30% decrease of $PM_{2.5}$ and O_3 levels in that period did not translate into statistically significant changes in premature mortality rates.[14] It is apparent that socially optimal levels of control, those that balance marginal benefits versus the marginal costs of abatement, cannot be designed solely on the basis of epidemiological data but will require information on the chemical and biological mechanisms of the adverse health effects induced by specific air pollutants.[15−18]

Inhaled pollutants (O_3, NO_2 and $PM_{2.5}$) are prevented from coming in contact with lung tissue by an epithelial lining fluid (ELF, 0.2−0.5 μm thick) exuded from underlying lung and resident immune cells.[19] ELF contains a suite of endogenous antioxidants (AO) such as glutathione (GSH), ascorbic and uric acids and α-tocopherol, of which GSH (∼100−500 μM) is the most abundant.[19−26] Inhaled oxidants, mainly but not exclusively O_3, may react as such with GSH or be converted into more reactive OH-radicals (·OH)[27,28] upon colliding with the ELF via Fenton-type chemistry.[23,29−32] Inhaled particulates are known to induce ·OH generation in ELF surrogates.[16,33−40] Much of the damage inflicted by superoxide $O_2^{\cdot-}$ and H_2O_2 in vivo is in fact due to their conversion into the more reactive ·OH in reactions catalyzed by transition metal ions.[41] Glutathione, in addition to ascorbate,[29] by being the most abundant and highly reactive ELF antioxidant both toward O_3 and ·OH at physiological pH, may be the main scavenger of polluted air oxidants and pro-oxidants.

It has long been considered that the main function of GSH is to scavenge exogenous oxidants into "ox-GSH" innocuous species. It was further believed that "ox-GSH" was the disulfide GSSG that would be produced from the recombination of the thiyl $GS^{\cdot-}$ radicals ensuing (S)−H atom abstraction by ·OH.[42−45] The current view is that scavenging has a dual

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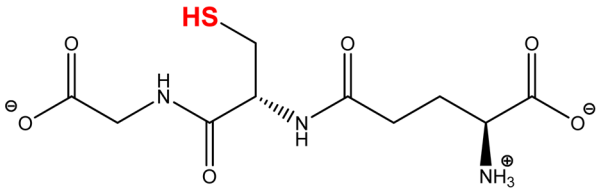
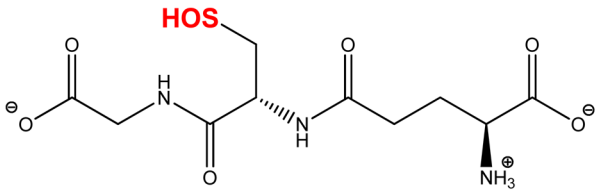
function in the sense that it not only deactivates powerful oxidants, but the [GSH]/["ox-GSH"] ratios generated in the ELF relay the intensity of oxidative stress to the immune system,[46−48] thereby unleashing systemic responses to external injury. A nonspecific systemic immune response to inhaled oxidants would be expected if they were converted into a common ·OH intermediate in the ELF,[49,50] and oxidative stress signaled by [GSH]/["ox-GSH"] ratios.[21,46,51−53] We have previously shown that the products of GSH[23] and cysteine[31] reactions with O_3(g) at the air−water interface are GSH-sulfonic, and Cys-sulfenic, Cys-sulfinic, and Cys-sulfonic acids rather than GSSG or CySSCy, respectively (Scheme 1).

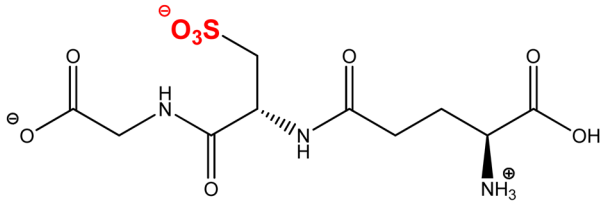
Scheme 1



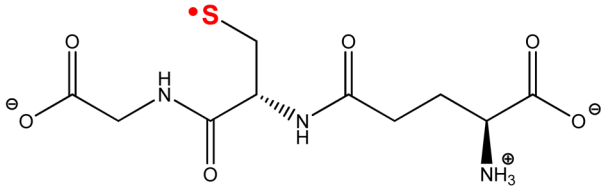
GSH^-, $C_{10}H_{16}N_3O_6S^-$, m/z: 306.08



$GSOH^-$, $C_{10}H_{16}N_3O_7S^-$, m/z: 322.07



GSO_3H^-, $C_{10}H_{16}N_3O_9S^-$, m/z: 354.06



$GS^{\bullet-}$, $C_{10}H_{15}N_3O_6S^{\bullet-}$, m/z: 305.07

We now report the results of experiments that identify, for the first time, the products of GSH oxidation by ·OH on the surface of aqueous solutions in air at 1 atm.

In our experiments, we investigate the initial stages of the chemical reactions taking place on the surface of aqueous GSH (γ-L-glutamyl-L-cysteinyl-glycine) and GSSG solutions briefly (≤50 μs) exposed to gas-phase OH-radicals. Reagents and products are simultaneously and unambiguously detected online via electrospray ionization mass spectrometry (ES-MS) of continuously flowing, fresh, dilute GSH and GSSG aqueous microjets collided with ·OH(g) pulses generated in the 266 nm laser photolysis of O_3 (into O_2 + $O(^1D)$) in $O_3/O_2/H_2O/N_2$ gas beams. In these events, ·OH(g) thermally accumulates on the surface of water, and then reacts with available substrates or terminates as H_2O_2.[54−57]

$$GSH + \cdot OH \rightarrow \text{products} \quad (R1)$$

$$\cdot OH + \cdot OH \rightarrow H_2O_2 \quad (R2)$$

The high reactivity of ·OH and its preference for the surface over bulk water[58,59] ensure that these processes take place in the outermost interfacial layers.[55,56] See the experimental section below and Supporting Information (SI) for details.

Figure 1 shows negative ion ES mass spectra of 100 μM GSH(aq) (pH 4.4) microjets alternatively exposed to $O_2/H_2O/N_2$ and $O_3/O_2/H_2O/N_2$ gas beams both in the dark and under laser pulses.

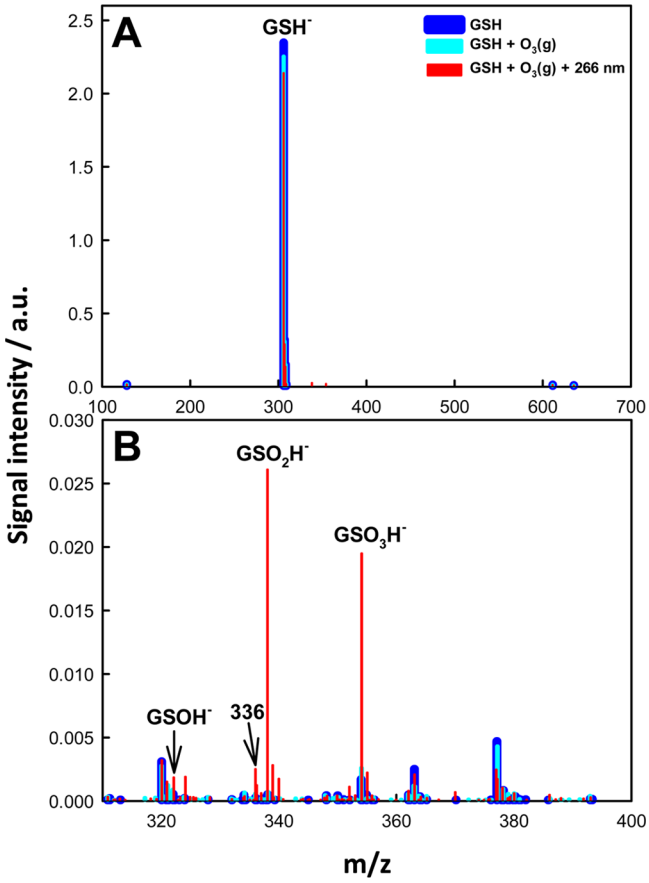


Figure 1. (A) Negative ion mass spectrum of aqueous 100 μM GSH (pH 4.4) microjets in $O_2/H_2O/N_2$(g) mixtures (blue) or exposed to ~80 ppmv O_3(g) without (cyan)/with (red) 40 mJ 266 nm pulses. ($[OH(g)]_0 \leq 8$ ppmv). 1 ppmv = 2.46 × 10^{13} molecules cm^{-3}. (B) Zoomed-in spectrum of oxidation products in the 310−400 Da range.

At pH 4.4, GSH is mostly present as the monoanion GSH^- ($m/z^- = 306$) of its glycine carboxylic group (pK_a = 3.7); the cysteine thiol −SH group (pK_a = 8.8) and the α-ammonium-glutamyl zwitterion moiety remain neutral (Scheme 1).[23,43] We verified that the addition of O_3(g) does not generate new signals, in accordance with our previous report on GSH^- inertness toward O_3 (cf. with GS^{2-} + O_3).[23] We also verified that GSH^- and $GSSG^-/GSSG^{2-}$ signals were not affected, nor

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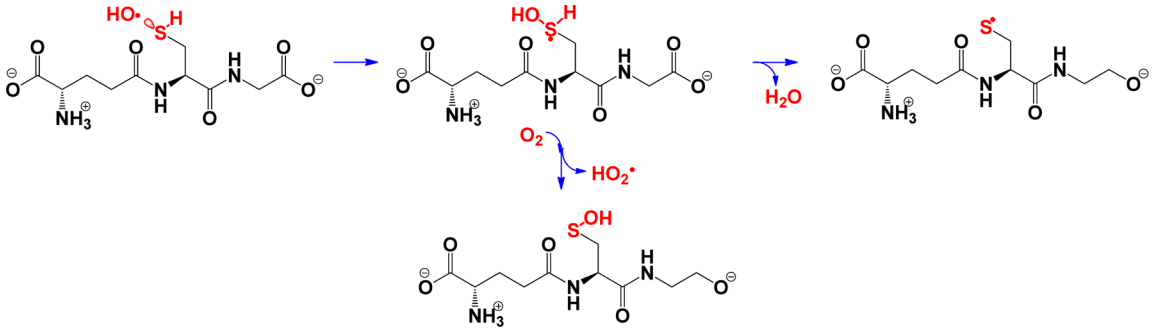
Scheme 2



did new signals appear under 266 nm pulses in the absence of O_3(g) (see SI, Figures S2 and S3).

Mass spectra change upon 266 nm irradiation of $O_3/O_2/H_2O/N_2$ gas beams: GSH^- signals decay as a function of laser energy (i.e., [·OH]) and new signals appear, which are therefore ascribed to products of (GSH^- + ·OH) reactions. The reaction GSH^- + ·OH in bulk water is diffusionally controlled: $k_1 \geq 3.5 \times 10^9$ M^{-1} s^{-1}.[43,60] We estimate $[\cdot OH(g)]_0 \sim 8$ ppmv at the spot where ·OH(g) are generated (see [·OH(g)] estimates in SI). We consider that 8 ppmv is an upper limit to [·OH] on the surface of microjets in the experiments of Figure 1. Note that exposures to 1 ppmv = 2.5×10^{13} molecules cm^{-3} (at 1 atm, 298 K) for $\tau \leq 10$ μs: $E = [\cdot OH(g)] \times \tau < 2.5 \times 10^8$ molecules cm^{-3} s, are much smaller than those in typical flow reactor experiments on ·OH(g) reactions: $E \geq 2 \times 10^{10}$ molecules cm^{-3} s.[55] The molecular formulas of products can be unambiguously inferred from their mass-to-charge ratios. Thus, the $m/z^- = 322 = 306 + 16$ signal is assigned to a sulfenic acid ($GSOH^-$), $m/z^- = 338 = 306 + 32$ to a sulfinic acid (GSO_2H^-), and $m/z^- = 354 = 306 + 48$ to a sulfonic acid (GSO_3H^-). We have previously found that the $m/z^- = 336 = 354-18$ signal results from collisionally induced loss of neutral H_2O from GSO_3H^-.[23] The GSO_nH ($n = 1-3$) acids correspond to 1, 2, and 3 O atom (2-electron) transfers to GSH^- (see Scheme 1), which seem to ensue from initial ·OH additions to reduced S-atoms followed by H-abstractions by O_2: $G(HO)(O)_{n-1}S-H^{\cdot -}$ + O_2 = $GSO_{n-1}OH^-$ + $HO_2\cdot$ (Scheme 2) and/or by ·OH: $G(HO)(O)_{n-1}S-H^{\cdot -}$ + ·OH = $GSO_{n-1}OH^-$ + H_2O.

$$GSH^- + \cdot OH \rightarrow GSH-OH^{\cdot -} \quad \text{(R3)}$$

$$GSH-OH^{\cdot -} + O_2 \rightarrow GSOH^- + HO_2\cdot \quad \text{(R4a)}$$

$$GSH-OH^{\cdot -} + \cdot OH \rightarrow GSOH^- + H_2O \quad \text{(R4b)}$$

Sulfenic acids are weak acids ($pK_a \approx 7-8$)[31] and should remain protonated at pH 4. The stronger sulfinic ($pK_a \sim 2$) and sulfonic acid ($pK_a < 1$), however, would replace the carboxylic acid in the glutamyl zwitterion (Scheme 1). To our knowledge, this is the first report on the direct detection of glutathione sulfenic and sulfinic acids at the air−water interface.

That the products we observe stem from ·OH-addition to S atoms rather than H-abstraction from S−H (or the pool of available N−H and C−H bonds),[61,62] is substantiated by the conspicuous absence of the species that should have appeared if the glutathiyl radical $GS^{\cdot -}$ ($m/z^- = 305$) had been produced via H-atom abstraction in the initial attack by ·OH.[43,63−67] If $GS^{\cdot -}$ had been present, since $k(GS^{\cdot -} + GSH^-) = 6.6 \times 10^7$ M^{-1} s^{-1},[43] $GS^{\cdot -}$ could have added to GSH^- into $GSS(H)G^{\cdot 2-}$: $GS^{\cdot -}$ + GSH^- = $GSS(H)G^{\cdot 2-}$, at [GSH] > 0.2 mM in $\tau_{1/2} \leq 0.69$ $[k(GS^{\cdot -} + GSH^-) \times [GSH^-]]^{-1} = 0.69$ $[6.6 \times 10^7$ M^{-1} $s^{-1} \times (2 \times 10^{-4}$ M$)]^{-1} = 50$ μs contact times. $GSS(H)G^{\cdot 2-}$ should have appeared at $m/z^- = (305 + 306)/2 = 611/2 = 305.5$, or at $m/z^- = 305 + 306 + 1 = 612$ if $GSS(H)G^{\cdot 2-}$ were protonated as $GSS(H_2)G^{\cdot -}$. Furthermore, possible intramolecular H-transfers in $GS^{\cdot -}$ could have given rise to isobaric carbon-centered radicals,[44] and to isobaric $m/z^- = 337$ peroxyl radicals. The latter could have been detected as such or after they had undergone recombination/disproportionation into carbonyls and alcohols, as we found in the case of mono- and dicarboxylic acids oxidations initiated by ·OH in this system.[55,56] The fact that none of above signals were detected, i.e., their signals remained below detection limits, in the [GSH] = (0.01−100) mM range (see Figures S4 and S5) represents strong evidence against H-atom abstraction from the thiol group, and the participation of $GS^{\cdot -}$ in this system. Present results stand in striking contrast with literature reports on the production of the $GSS(H_2)G^{\cdot -}$ ($GSSG^{\cdot -}$ in the literature) disulfide in the oxidation of GSH by ·OH generated by pulse radiolysis in bulk aqueous solutions.[43,65,68,69] Undetectable disulfide GSSG signals, which should have appeared at $m/z = 305$ (dianion) and 611 (monoanion) even in 100 mM GSH, also precludes the following condensation reaction:

$$GSOH^- + GSH^- \rightarrow GSSG^{2-} + H_2O \quad \text{(R5)}$$

Figure 2 shows ES mass spectral signals from aqueous 100 μM GSH microjets exposed to irradiated $O_3/O_2/H_2O/N_2$ mixtures as a function of pulse energy (i.e., [·OH]). In Figure 2, laser energies at 1, 5, 10, 20, 30, and 40 mJ $pulse^{-1}$ correspond to $[\cdot OH(g)]_0 \approx 0.5$, 2.7, 5.1, 9.4, 13.1, and 16.2 ppmv, which, from the mean ·OH speed $c = 6.09 \times 10^4$ cm s^{-1} at 298 K, correspond to 0.2×10^{18}, 1.0×10^{18}, 1.9×10^{18}, 3.5×10^{18}, 4.9×10^{18} and 6.1×10^{18} molecules cm^{-2} s^{-1} fluxes on the surface of the microjets, respectively. It is apparent that above a certain ·OH dose, GSH^- is depleted in the outermost interfacial layers, whereupon excess ·OH recombines into relatively unreactive H_2O_2 toward the GSH^- remaining in underlying layers (R2).[55,56] We have observed the same behavior in the oxidation of mono- and dicarboxylic acids initiated by ·OH at the air−water interface under similar conditions.[55,56] The limited depletion of GSH^- under excess ·OH represents direct evidence that we observe a truly interfacial reaction taking place in the outermost water layers.

We also performed experiments in which aqueous GSH solutions containing Fe^{2+} at pH ~ 4 were exposed to O_3(g) in the absence of 266 nm irradiation. Recall that at pH 4, GSH is present as the inert monoanion GSH^- toward O_3(g).[23] Previous experiments in our laboratory have shown that the exposure of Fe^{2+} solutions to O_3(g) generates reactive mono-

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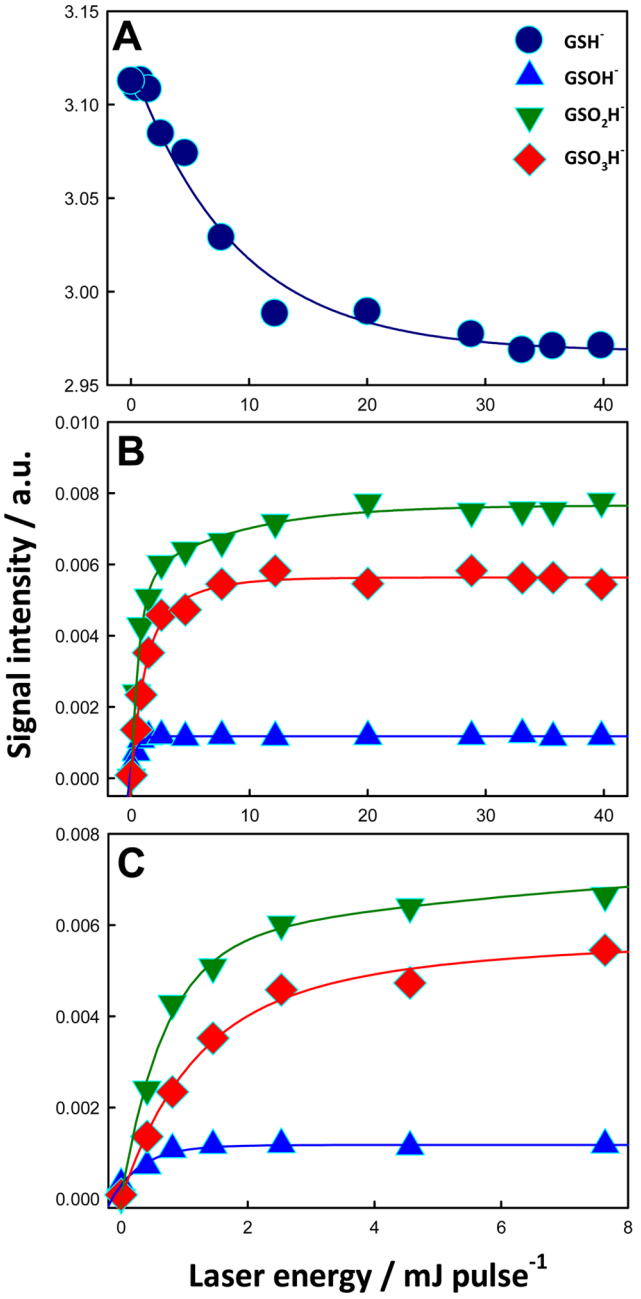

Figure 2. Reactant (A) and products (B) mass spectral signal intensities from aqueous 100 μM GSH (pH 4.4) microjets exposed to $O_3/O_2/H_2O/N_2$(g) mixtures at $[O_3(g)] \sim 170$ ppmv, irradiated with 266 nm laser beams as functions of laser energy (in mJ pulse^{-1}). (C) Zoomed-in B data at lower laser energies.

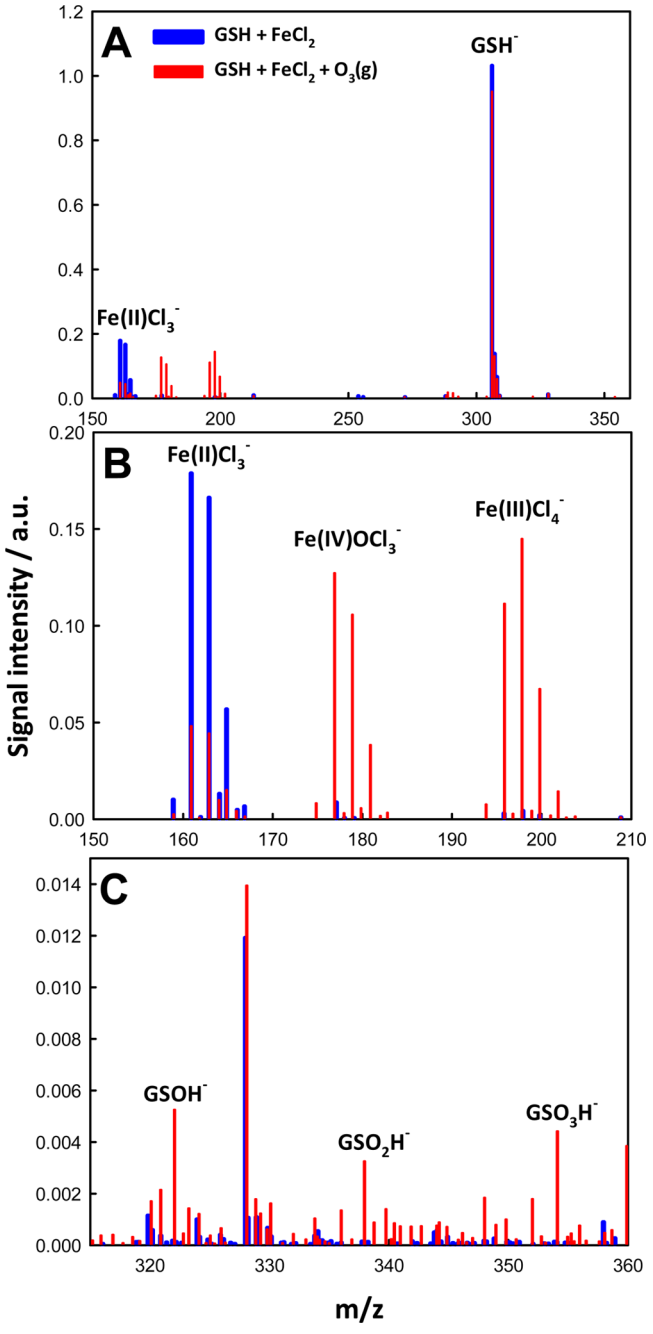

Figure 3. (A) Negative ion mass spectrum of aqueous 500 μM (GSH + $FeCl_2$) mixture (pH 4.3) microjets in $O_2/H_2O/N_2$(g) mixtures (blue) or exposed to ~360 ppmv O_3(g) (red). 1 ppmv = 2.46×10^{13} molecules cm^{-3}. (B) Zoomed-in spectrum of oxidation products in the 150−210 Da range. (C) Zoomed-in spectrum of oxidation products in the 315−360 Da range.

and poly nuclear O═Fe(IV) oxo-ferryl species[27] and, possibly, some ·OH.[28] Figure 3 shows that in the presence of Fe^{2+} as catalyst, O_3(g) can oxidize GSH^- to sulfenic, sulfinic, and sulfonic acids *even in acidic media* via the reactive intermediates generated in fast Fenton-type chemistry at the air−water interface.[27]

These experiments show that the presence of transition metals in ELF's, possibly carried by inhaled particulates,[70] extends the reactivity of O_3(g) towards GSH into media that are more acidic than the normal circumneutral physiological range. This finding is relevant to certain pathologies, such as asthma, which are known to acidify the respiratory tract,[41,46,53,71] and to the mechanism of the synergistic adverse health effects of O_3 and particulates.[6,72−74] The inability of glutathione to scavenge O_3 in acidic media[23] in the absence of Fe^{2+} is compensated by ascorbic acid.[29] However, at pH < 5 ascorbic acid scavenges O_3(g) into a toxic ozonide rather than innocuous dehydroascorbic acid as it does in neutral media.[29]

The question of whether GSSG could have been formed in the oxidation of GSH but went undetected because it might be rapidly consumed under present conditions is now addressed. Figure 4 shows negative ion ES mass spectra of 100 μM

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J. Phys. Chem. Lett. 2015, 6, 3935−3943

GSSG(aq) microjets exposed to $O_2(g)/H_2O(g)/N_2(g)$, and to $O_3(g)/O_2(g)/H_2O(g)/N_2(g)$ with the 266 nm laser on and off.

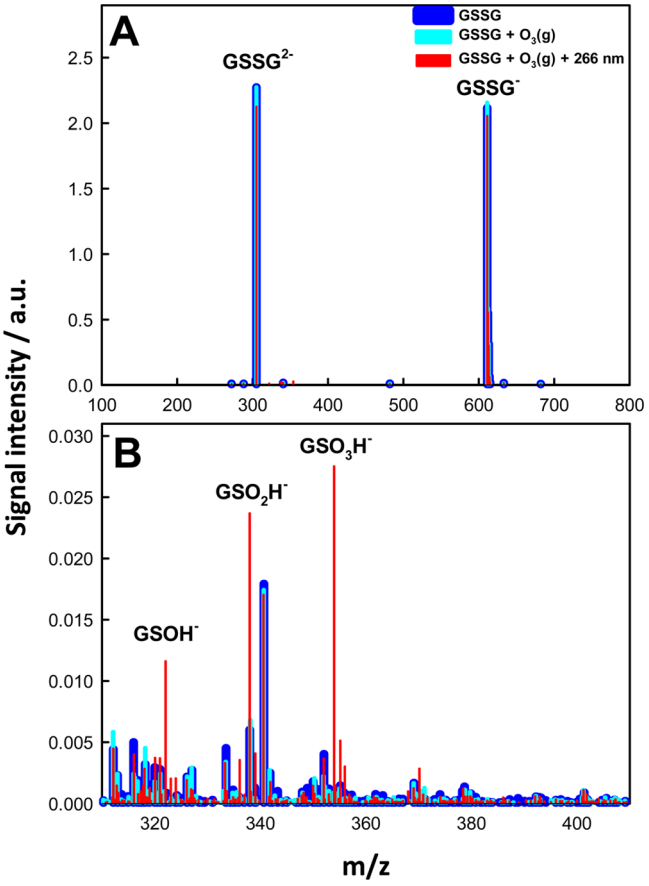

Figure 4. (A) Negative ion mass spectrum of 100 μM GSSG (pH 4.3) aqueous microjets exposed to ~70 ppmv $O_3(g)$ in $O_2/H_2O/N_2(g)$ mixtures without (cyan)/with (red) 40 mJ 266 nm pulses. ($[OH(g)]_0 \leq 6$ ppmv). 1 ppmv = 2.46 × 10^{13} molecules cm^{-3}. (B) Zoomed-in spectrum of oxidation products in the 310−410 Da range.

Figure 5 shows mass spectral signals of reactants and products as functions of pulse energy. At pH 4.3, GSSG is present both as monoanion $GSSG^-$ ($m/z^- = 611$) and dianion $GSSG^{2-}$ ($m/z^{2-} = 305$), which are inert toward $O_3(g)$ (cyan traces in Figure 4A,B) in accordance with our previous study.[23] In the presence of ·OH, however, product signals appear at $m/z^- = 322$, 338 and 354, i.e., the same as those observed in the GSH^- + ·OH reaction (Figure 1). It is key to note, however, that relative product signal intensities $GSO_3H^- > GSO_2H^- > GSOH^-$ in the $GSSG^-$ + ·OH reaction (Figure 5C) differ from those $GSO_2H^- > GSO_3H^- \gg GSOH^-$ in the GSH^- + ·OH reaction (Figure 2C). These findings are consistent with the rapid, sequential oxidation of GSH^- by ·OH into $GSOH^-$ and GSO_2H^-, and the fact that $GSOH^-$ is a primary product of the $GSSG^-$ + ·OH reaction (Scheme 3) rather than a second-generation species, as is the case from GSH^- + ·OH (Scheme 2).

The above observations are consistent with a mechanism involving the addition of ·OH to S atoms into a discrete radical adduct HO−S(·)−H, which reacts with O_2/·OH leading to sulfoacids −SOH (+ HO_2·/H_2O) or, in its absence, may decompose into thiyl −S· radicals (+ H_2O).[75] Note that the fraction of $GS^{\cdot-}$ (generated in the decomposition of the initial

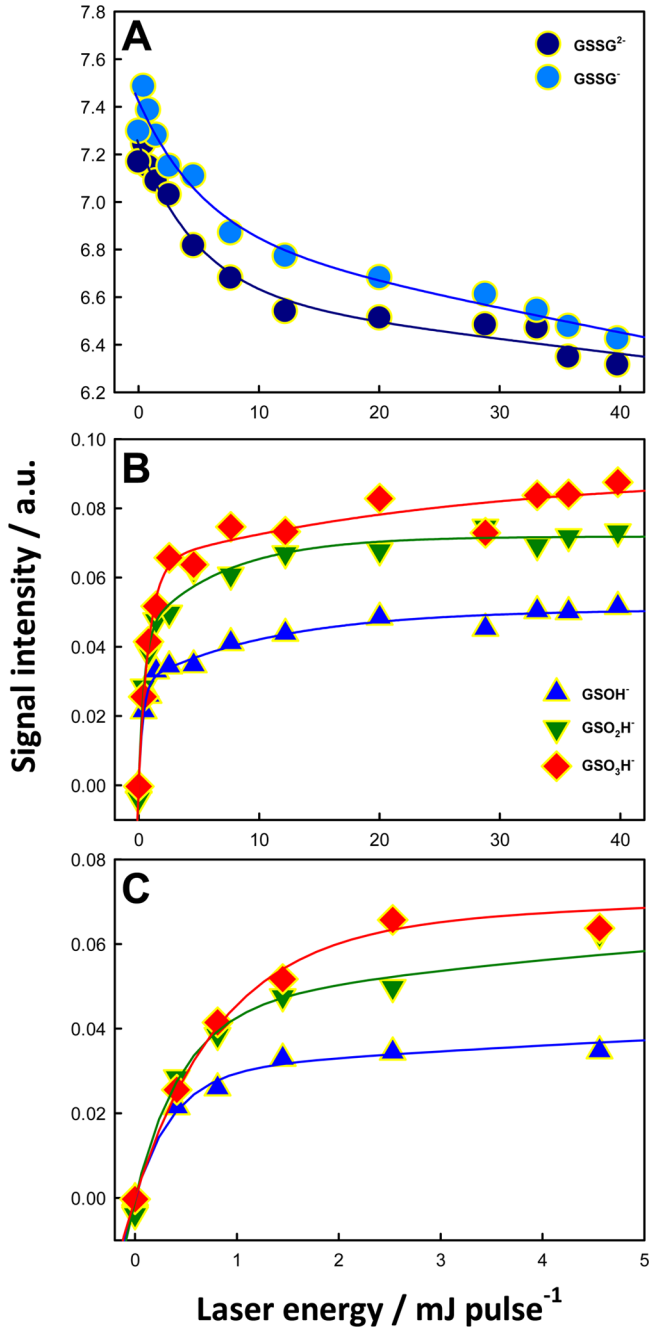

Figure 5. Reactant (A) and products (B) mass spectral signal intensities from aqueous 100 μM GSSG (pH 4.1) microjets exposed to $O_3/O_2/H_2O/N_2(g)$ mixtures at $[O_3(g)] \sim 130$ ppmv, irradiated with 266 nm laser beams as functions of laser energy (in mJ $pulse^{-1}$). (C) Zoomed-in of B data at lower laser energies.

GSSG−$OH^{\cdot-}$ adduct) in equilibrium with its peroxyl GS-$OO^{\cdot-}$ radical ($m/z^- = 337$) in water saturated with air ($[O_2(aq)] = 2.6 \times 10^{-4}$ M) is given by $[GS\text{-}OO^{\cdot-}]/[GS^{\cdot-}] = K_{GS^{\cdot-}+O2} \times [O_2(aq)] = 3.2 \times 10^3\ M^{-1} \times 2.6 \times 10^{-4}\ M = 0.8$.[66] The absence of $m/z^- = 337$ signals in Figure 4B therefore indicates that $GS^{\cdot-}$ is rapidly converted into the sulfenic acid $GSOH^-$ by excess ·OH. Again, there is no evidence of the formation of products initiated by H-atom abstraction from C−H/N−H groups.

The extraordinary specificity of ·OH for adding to the glutathione thiol −SH sulfur atom at the air−water interface, bypassing exothermic (and fast, both in gas-phase or bulk

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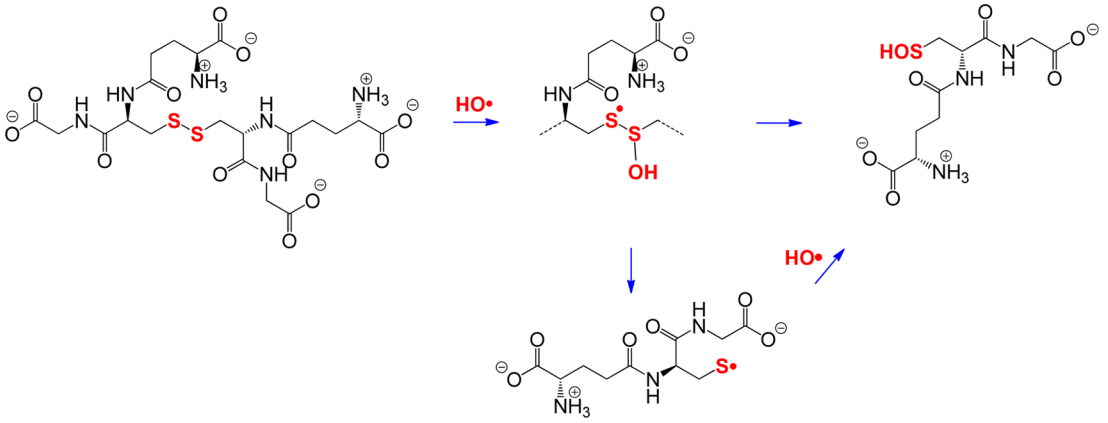
Scheme 3



water) H-abstractions from S−H itself and the myriad C−H and N−H bonds available in glutathione,[43,51,52,64,66,67,76,77] evokes a recent theoretical radical recognition and steering mechanism in which ·OH is captured by the host GSH anionic carboxylic groups and directed toward the reactive −SH group by a concerted process involving multiple H-bonded interactions within a flexible GSH framework.[68,78] The issue of whether the ·OH so positioned would directly H-abstract from S−H, thereby producing the $GS^{\cdot-}$ thiyl radical in one step, or add to the S-atom into a discrete, long-lived intermediate $GS(H)OH^{\cdot-}$ that could react with other molecules has recently been addressed by high-level MP4 ab initio calculations for the CH_3SH + ·OH reaction.[75,79−81] It was found that CH_3SH + ·OH bind into a covalent $CH_3S(H)OH\cdot$ adduct that lies about 3.5 kcal mol^{-1} below the reactants.[75] This study, although predicting a significantly smaller stabilization than the 13 kcal mol^{-1} value derived from gas-phase kinetic experiments on CH_3SH + ·OH,[82] supports the existence of the discrete intermediate implied by our experiments. We wish to point out that previous experiments have shown that O_3 reacts with various substrates at the air−water interface via O-atom (two-electron) rather than thermodynamically allowed one-electron transfers, and at much faster rates than those estimated from reaction rate constants in bulk water and $[O_3(aq)]$ deduced from its Henry's law constant (H = 0.01 M atm^{-1}).[27,29,32] The suggestion was made that the steep water density gradient and the peculiar structure of interfacial water modifies the course of reactions by enabling oxidants (such as ·OH in the present case, and O_3 in Fenton's reaction[27]) to reach emerging functional groups, such as the glutathione thiol, relatively unencumbered by solvation water molecules.[27,83]

Summing up, in moderately acidic (pH ≤ 5) media, such as those created by diverse pathologies, which include asthma[71,84] and the systemic immune response to inhaled particulates,[85] glutathione GSH^- is found to be oxidized by ·OH into sulfenic acid $GSOH^-$, sulfinic GSO_2H^- and sulfonic GSO_3H^- acids[86−89] with remarkable specificity. This is the first report on the direct detection of glutathione sulfenic and sulfinic acids at the air−water interface. The exceptional specificity of ·OH on the surface of water versus its lack of selectivity in bulk water implicates an unprecedented molecular recognition process during [OH···GSH] interfacial encounters. The ·OH implicated in these events may be generated in situ from inhaled O_3 in the presence of transition metal ions such as Fe^{2+}, in addition to endogenous sources. Since both the cysteine sulfenic and sulfinic acid functionalities are reduced enzymatically back to the thiol by NADPH in vivo,[47,87,89] our results suggest that redox balance and signal transduction by ELF glutathione involve sulfur oxoacids rather than a disulfide.

EXPERIMENTAL SECTION

The experimental setup has been described in a previous publication.[55] Here we summarize specific features of the setup used in the experiments reported herein. The charged product species generated on the surface of GSH(aq) or GSSG(aq) microjets during $\tau \sim 10-50$ μs contact times (τ is the lifetime of the microjets before they are pneumatically nebulized into smaller droplets) with $O_3(g)$ or ·OH(g) beams are monitored in situ by an ES-MS (Agilent 6130 Quadrupole LC/MS Electrospray System, Kyoto University).[55] Samples are injected at 100 μL min^{-1} into the spraying chamber of the mass spectrometer through a grounded stainless steel needle (100 μm bore) coaxial with a sheath issuing nebulizer $N_2(g)$ at subsonic velocities ($v_g \sim 160$ m/s).[90] The surface specificity of our experiments had been demonstrated previously.[27,90] Note that the products we observe are formed when gaseous reactants collide with the intact aqueous jets as they emerge from the nozzle, i.e., before jets are broken up into submicron charged droplets by the nebulizer gas.[27] Since 266 nm pulses flash every 100 ms, and microjets break up within 10−50 μs after being ejected from the nozzle, we assume that the observed phenomena take place in fresh solutions.[55] See SI for further details.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jpclett.5b01819.

Additional data and experimental details (PDF)

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Notes

The authors declare no competing financial interest.

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